

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0098435-Wguc	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 07556	International filing date (day/month/year) 08/10/1999	(Earliest) Priority Date (day/month/year) 19/10/1998
Applicant MERCK PATENT GMBH et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the International search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the International search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

NATURAL FORMULATION FOR THE TREATMENT AND PREVENTION OF DEPRESSION, CONTAINING ST JOHN'S WORT AND DERIVATIVES OF DIHYDRO- AND TETRAHYDROFOLIC ACID

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

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(PCT Article 18 and Rules 43 and 44)

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Applicant MERCK PATENT GMBH et al.		

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This International Search Report consists of a total of 3 sheets.

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1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

NATURAL FORMULATION FOR THE TREATMENT AND PREVENTION OF DEPRESSION, CONTAINING ST JOHN'S WORT AND DERIVATIVES OF DIHYDRO- AND TETRAHYDROFOLIC ACID

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 07556

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8 and 9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8 and 9
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07556

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K35/78 //(A61K35/78,31:505)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 820 867 A (BEWICKE CALVERLY M) 13 October 1998 (1998-10-13) claims	1-9
P, X	--- WO 99 37155 A (NUTRAMAX LAB INC) 29 July 1999 (1999-07-29) claims 1-3 -----	1
<div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Further documents are listed in the continuation of box C. </div> <div> <input checked="" type="checkbox"/> Patent family members are listed in annex. </div> </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">14 March 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">22/03/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Leherte, C</div>

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5820867 A	13-10-1998	NONE	
WO 9937155 A	29-07-1999	AU 2470299 A	09-08-1999

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PCT INTERNATIONAL COOPERATION TREATY

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

MERCK PATENT GMBH
Frankfurter Strasse 250
D-64293 Darmstadt
ALLEMAGNE

Date of mailing (day/month/year)

11 February 2000 (11.02.00)

Applicant's or agent's file reference

0098435-Wguc

IMPORTANT NOTIFICATION

International application No.

PCT/EP99/07556

International filing date (day/month/year)

08 October 1999 (08.10.99)

Applicant

MERCK PATENT GMBH et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. ☒ **Correction of priority claim.** In accordance with the applicant's notice received on: 26 January 2000 (26.01.00), the following priority claim has been corrected to read as follows:
US 19 October 1998 (19.10.98) 60/104,710
☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:
☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ **Priority claim considered not to have been made.**
☐ The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.
The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).
5. ☐ In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):
6. A copy of this notification has been sent to the receiving Office and
☒ to the International Searching Authority (where the international search report has not yet been issued).
☒ the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

P. Regis

Telephone No. (41-22) 338.83.38

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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 May 2000 (18.05.00)	
International application No. PCT/EP99/07556	Applicant's or agent's file reference 0098435-Wguc
International filing date (day/month/year) 08 October 1999 (08.10.99)	Priority date (day/month/year) 19 October 1998 (19.10.98)
Applicant BUCHHOLZ, Herwig et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

22 March 2000 (22.03.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer F. Baechler Telephone No.: (41-22) 338.83.38
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REC'D 31 OCT 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0098435-Wguc	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/07556	International filing date (day/month/year) 08/10/1999	Priority date (day/month/year) 19/10/1998
International Patent Classification (IPC) or national classification and IPC A61K35/78		
Applicant MERCK PATENT GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 22/03/2000	Date of completion of this report 27.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cattell, James Telephone No. +49 89 2399 8468 

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07556

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-7 as originally filed

Claims, No.:

1-9 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-9
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-9
Industrial applicability (IA)	Yes:	Claims 1-9
	No:	Claims

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/07556

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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V.

- 1). Document D1 (US5,820,867) describes the combination of an extract of St.John's Wort and folic acid to treat depression.

The claimed use of di hydro and tetrahydro folic acid is novel over this disclosure (Art 33(2) PCT).

However, in the knowledge of the folate cycle, the skilled man would consider these substances as obvious alternatives to folic acid. No inventive step can therefore presently be recognised.

VIII.

- 2). For the assessment of the present claims 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A01N 57/00, 57/26, 43/58, 43/60, 43/90, 37/00, 37/12, 37/44, 35/00, A61K 31/66, 31/685, 31/66, 31/495, 31/50, 31/52, 31/20, 31/195, 31/12	A1	(11) International Publication Number: WO 99/37155 (43) International Publication Date: 29 July 1999 (29.07.99)
(21) International Application Number: PCT/US99/01581 (22) International Filing Date: 26 January 1999 (26.01.99) (30) Priority Data: 60/072,721 27 January 1998 (27.01.98) US 60/075,998 26 February 1998 (26.02.98) US 60/112,993 18 December 1998 (18.12.98) US (71) Applicant: NUTRAMAX LABORATORIES, INC. [US/US]; 2208 Lakeside Boulevard, Edgewood, MD 21040 (US). (72) Inventors: HENDERSON, Todd, R.; 1604 Randallwood Court, Jarrettsville, MD 21084 (US). CORSON, Barbara, E.; 225 Kinkle Road, Fawn Grove, PA 17321 (US). (74) Agents: BERMAN, Paul, J. et al.; 1201 Pennsylvania Avenue, N.W., P.O. Box 7566, Washington, DC 20044-7566 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMBINATIONS OF TYROSINE, METHYLATING AGENTS, PHOSPHOLIPIDS, FATTY ACIDS, AND ST. JOHN'S WORT FOR THE TREATMENT OF MENTAL DISTURBANCES (57) Abstract This invention provides therapeutic compositions for the treatment or prevention of mental disturbances such as depressive states and for regulating the level of certain neurotransmitters and thereby improving the function of the central nervous system and cognitive function in humans and other animals. The therapeutic compositions comprise any two or more of tyrosine, one or more methylating agents, one or more phospholipids, one or more fatty acids and St. John's Wort (<i>Hypericum perforatum</i>), whether naturally, synthetically, or semi-synthetically derived. The invention also provides a method of administering these compositions to humans or animals in need thereof.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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COMBINATIONS OF TYROSINE, METHYLATING AGENTS, PHOSPHOLIPIDS,
FATTY ACIDS, AND ST. JOHN'S WORT FOR THE TREATMENT OF MENTAL
DISTURBANCES

5

Inventors: Todd R. Henderson, DVM and Barbara E. Corson, V.M.D.

Field of the Invention

10

The present invention relates to the field of neurohormonal, cognitive and antidepressive therapy. More particularly, the invention pertains to combinations of two or more compounds selected from the group consisting of tyrosine, one or more methylating agents, one or more phospholipids, one or more fatty acids, and St. John's Wort (*Hypericum perforatum*), whether naturally, synthetically, or semi-synthetically derived, for use in such therapy.

15

Background of the Invention

20

In the mammalian nervous system, nerve impulses are carried across synapses by chemical mediators called neurotransmitters. These compounds are synthesized and stored in the neuron itself, and released into the synaptic cleft. After binding to the post-synaptic neuron, the neurotransmitter is rapidly destroyed or removed, thus terminating its effect. By controlling the synthesis, storage, release, and destruction of neurotransmitters, the body is normally able to control nervous system function. Conversely, derangements in neurotransmitter function cause abnormalities in the functioning of the nervous system. Defective neurotransmission can result from problems with axonal transport, neuronal membrane permeability, lack of precursor substances, or with biosynthesis, release, or inactivation of neurotransmitters. The causes

25

of such derangements of normal neural physiology are as yet incompletely understood.

Guyton, A. and Hall, J., Textbook of Medical Physiology, 9th ed., WB Saunders, 1996, pp. 565-82. It is becoming increasingly clear, however, that the manipulation of neuronal processes can serve as a tool for controlling nervous system function. Stein, M., et al., *In Vivo and In Vitro Modulation of Central Type Benzodiazepine Receptors by Phosphatidylserine*, Molecular Brain Research 5 (1989), pp. 9-15.

Disturbances of mood are increasingly common in western civilization. Although these disturbances have previously been regarded as a sign of "weakness," science is now aware that these disorders are indeed caused by imbalances in the functions of neurons and the neurotransmitters that they synthesize. At present, several classes of pharmaceuticals are used to treat depression. Serotonin is sometimes called the "feel-good" neurotransmitter: levels of serotonin correlate closely with mood. Increasing serotonin levels in the synaptic cleft results in mood elevation. The selective serotonin reuptake inhibitor pharmaceuticals ("SSRIs") slow down the process by which serotonin is inactivated (FIG. 1), and thereby increase the level of serotonin within the synaptic cleft. The monoamine oxidase inhibitors ("MOA inhibitors") inhibit one of the two steps in the enzymatic catabolism of serotonin and the catecholamines (dopamine, epinephrine and norepinephrine) (FIG. 1). Several forms of depression and other CNS diseases (e.g., Parkinson's disease) have been associated with low levels of these neurotransmitters. This inhibition results in an increased level of these neurotransmitters within the synaptic cleft.

Although the SSRIs and the MOA inhibitors have proved of great benefit in the treatment of mental disturbances, both have side effects that preclude their use by some individuals. Side effects commonly seen include anxiety, insomnia, allergic reactions

[fluoxetine HCl (tradename, "Prozac")], and autonomic nervous system disorders including impotence, somnolence, diarrhea, and nausea [sertraline HCl (tradename, "Zoloft")]. Physicians Desk Reference, Medical Economics Co., Inc., Montvale, N.J., 1999, pp. 924-28, 2443-48.

5 Aging is often attended by a decrease in cognitive abilities. As the population ages, the need to address this problem without producing harmful side effects will increase. Normal cognition requires many of the same neurotransmitters and biomechanisms that are involved in mood regulation, such as serotonin and the catecholamines. Therefore, therapies that address normalization of neurotransmission
10 (that is, such therapies that would enhance the structure and function of the cell membrane, the production and release of neurotransmitters, and the well-regulated re-uptake or degradation of these neurotransmitters) will improve cognitive CNS function as well as mood. Although, as discussed above, pharmaceuticals exist for the correction of mood disorders, less attention historically has been directed towards the improvement of
15 cognition. Products such as preparations of *Ginkgo biloba* are available, which are theorized to affect blood supply to the brain, but which have not been shown to address other disorders.

 Many age-related neurochemical changes can be traced to structural and functional alterations in neuronal membranes. Specifically, the amount of
20 phosphatidylcholine and phosphatidylethanolamine in the cell membrane decreases with age. These membrane changes, in turn, have been related to changes in phospholipid content in the aging brain. Exogenous administration of phospholipids such as phosphatidylserine may prevent or reverse age-related neurochemical deficits, and has been used to treat such conditions. Champ, P. and Harvey, R., Biochemistry, 2nd ed.,

Lippincott, Philadelphia, 1994, pp. 266-7; Calderini, G., et al., *Phospholipids as Pharmacological Tools in the Aging Brain, Phospholipids in the Nervous System, Physiological Roles*, vol. 2: EdL LA Horrocks, Raven Press, New York, N.Y. 1985, p. 11; Bruni, A., et al., *Serine Phospholipids in Cell Communication*, Phospholipid Research and the Nervous System, LA Horrocks, eds., Laviana Press, Padova, 1986, p. 216; Sun, A. and Sun, G., *Neurochemical Aspects of the Membrane Hypothesis of Aging*, Interdiscipl. Topics Geront., vol. 15, Karfer, Basel, 1979, pp. 34-53; Pedata, F., et al., *Phosphatidylserine Increases Acetylcholine Release from Cortical Slices in Aged Rats*, Neurobiology of Aging, vol. 6, 1985, pp. 337-39; Crook, T., et al., *Effects of Phosphatidylserine in Age-Associated Memory Impairment*, Neurology 41, 1991, p. 644.

Prior art treatments are also limited in their effectiveness because they typically address only one element of CNS function, such as serotonin re-uptake or cerebral blood supply. A composition with multiple mechanisms of action would be an improvement over such prior art treatments because CNS function could be maximally enhanced while doses are minimized. For example, elevation of the serotonin levels in the synaptic cleft will increase the likelihood of serotonin/receptor binding to a certain extent. Cell membrane changes, however, may limit the activity of the receptor. The effects of increasing serotonin levels therefore may be enhanced or even optimized by also improving cell membrane and receptor function. Minimizing doses will also decrease the likelihood of adverse reactions or side effects. There is one currently-available pharmaceutical product (tradename, "Sinemet," by DuPont) that functions to increase the dopamine levels through two different mechanisms of action. The product contains levodopa, a precursor of dopamine, and carbidopa, which slows the breakdown of dopamine. This product has no effect, however, on membrane fluidity, nor does it

enhance the binding of dopamine with receptors. There is a need in the art, therefore, for a composition that combines multiple mechanisms of action to increase levels of dopamine and serotonin, facilitate binding of the neurotransmitters with neuronal cell membranes, and prevent premature deactivation of the neurotransmitters in the CNS, and
5 at the same time contains ingredients having a wide margin of safety and reduced or minimal side effects.

Summary of the Invention

It is a primary object of the invention to provide therapeutic and prophylactic compositions that will increase levels of dopamine and serotonin in those individuals
10 suffering from a deficiency of these neurotransmitters, and also improve neuronal cell membrane fluidity, thus enhancing receptor/ligand binding.

It is a further object of the present invention to provide such compositions which result in a low incidence of side effects.

It is a still further object of the present invention to provide a method of regulating
15 and/or improving the levels and function of certain neurotransmitters by administering the compositions of the present invention to humans or other animals in need thereof.

The present invention provides novel compositions and methods for regulating the level of certain neurotransmitters and thereby improving the function of the central nervous system in humans or other animals in need thereof. The compositions of the
20 invention comprise two or more compounds selected from the group consisting of tyrosine, methylating agents, phospholipids, fatty acids and St. John's Wort (*Hypericum perforatum*), whether naturally, synthetically, or semi-synthetically derived, for use in the facilitation of improved neurotransmitter levels and function in humans or animals.

Combinations containing methylating agents, phospholipids and/or fatty acids may contain one or more of each such class of compounds.

Brief Description of the Drawings

5

FIG. 1 is a sequence for the degradation of dopamine.

FIG. 2 is the molecular structure of tyrosine.

10

FIG. 3 is a sequence for the biosynthesis of catecholamines from tyrosine.

FIG. 4 is the molecular structure of S-adenosylmethionine.

FIG. 5 is the molecular structure of 5-methyltetrahydrofolate.

15

FIG. 6 shows the synthesis of phosphatidylcholine from phosphatidylserine.

Detailed Description of the Invention

In accordance with the teachings of the present invention, disclosed herein are
20 therapeutic and/or prophylactic compositions capable of increasing the levels and
function of certain neurotransmitters in the mammalian CNS and thereby treating or
preventing certain diseases associated with or resulting in deficiencies in levels or
function of those neurotransmitters and improving the structure and function of the
mammalian CNS. The invention relates to novel compositions comprising two or more
25 compounds selected from the group consisting of tyrosine, one or more methylating
agents, one or more phospholipids, one or more fatty acids and extracts of *Hypericum
perforatum* (St. John's Wort), whether naturally, synthetically or semi-synthetically
derived.

The amino acid tyrosine (FIG. 2) is important to central nervous system ("CNS") function because it is a precursor of the neurotransmitters dopamine, norepinephrine and epinephrine (FIG. 3). Champ and Harvey, *Biochemistry*, 1994. It is well established that tyrosine intake can directly affect levels of these neurotransmitters. Tyrosine is also a constituent of the enkephalins and endorphins, which function as natural painkillers and mood regulators. Tyrosine increases the levels of these neurotransmitters in the body. Braverman, E., *Tyrosine, The Healing Nutrients Within*, Keats Publishing, New Canaan, Conn., p. 44; Costanzo, L., *Physiology*, Williams and Wilkins, 1995, p. 16; Jahng, J., et al., *Differential Expression of Monoamine Oxidase A, Serotonin Transporter, Tyrosine Hydrosylase and Norepinephrine Transporter mRNA by Anorexia Mutation and Food Deprivation*, *Brain Res. Dev.* 107(2), 1998, pp. 241-46; Champ and Harvey, *Biochemistry*, 1994. Tyrosine is indicated in diseases associated with a deficit of these neurotransmitters, including Parkinson's disease and attention deficit disorder.

Methylating agents are essential for numerous reactions in the brain including maintaining cell membranes and synthesis of neurotransmitters. Decrease in levels of the methylating agents S-adenosylmethionine ("SAME") and 5-methyltetrahydrofolate ("5-MTHF") has been associated with age-related neurologic deficits and numerous psychiatric disorders, particularly depressive states. SAME is a compound synthesized in the body from adenosine triphosphate ("ATP") and methionine (FIG. 4). It is present in many tissues, including the central nervous system. The primary CNS function of SAME is to donate methyl groups in the reactions synthesizing various crucial compounds, including neurotransmitters and phospholipids. For example, SAME facilitates the conversion of phosphatidylethanolamine to phosphatidylcholine, which forms part of the inner, lipid layer of the plasma membrane. In so doing, SAME increases membrane

fluidity and enhances effectiveness of receptor/ligand binding. (Champ and Harvey, Biochemistry, 1994; Stramentinoli, G., *Pharmacologic Aspects of S-Adenosylmethionine*, American Journal of Medicine 83 (5A), 1987, p. 35; Baldessarini, F., *Neuropharmacology of S-Adenosyl Methionine*, American Journal of Medicine 83 (5A), 1987, p. 95; Carney, M., *Neuropharmacology of S-Adenosyl Methionine*, Clinical Neuropharmacology 9(3), 1986, p. 235; Janicak, P., *S-Adenosylmethionine in Depression*, Alabama Journal of Medical Sciences 25(3), 1988, p. 306. These functions may also pertain to other methyl donors such as betaine (trimethylglycine), 5-methyltetrahydrofolate, folic acid, and dimethylglycine. Champ and Harvey, Biochemistry, 1994.

The methylating agent 5-methyltetrahydrofolate ("5-MTHF") (FIG. 5), which is the active form of folate, has advantages over some other methylating agents, such as folic acid, because it can cross the blood-brain barrier. Unlike folic acid, 5-MTHF does not mask vitamin B-12 deficiency (pernicious anemia). It is absorbed and utilized in the body without being transformed. Moreover, 5-MTHF has the important role of converting homocysteine into methionine. Hyperhomocysteinemia has been implicated in hypercholesterolemia and vascular diseases, and 5-MTHF is a valuable compound for the treatment of these significant conditions. Champ and Harvey, Biochemistry, 1994; Abou-Saleh, M., *The Biology of Folate in Depression: Implications for Nutritional Hypothesis of the Psychoses*, J. Psychiatr. Res. 20(2), 1986, pp. 91-101; Matthews, R., et al., *Methylenetetrahydrofolate Reductase and Methionine Synthase: Biochemistry and Molecular Biology*, Eur. J. Pediatr. 157(2), 1998, pp. S54-59; Stramentinoli G., *General Information on 5-MTHF*, Knoll Farmaceutici Spa, unpublished material which may be obtained from the author at Via Fosse Ardeatine, 2-1-20060 Liscate (Mi); Loehrer, F., et

al., *Influence of Oral S-Adenosylmethionine on Plasma 5-Methyltetrahydrofolate, S-Adenosylhomocysteine, Homocysteine and Methionine in Healthy Humans*, J. Pharmacol. Exp. Ther. 282(2), 1997, pp. 845-50; Verhaar, M., *5-Methyltetrahydrofolate, the Active Form of Folic Acid, Restores Endothelial Function in Familial Hypercholesterolemia*, Circulation 27(3), 1998, pp. 237-41.

It is expected that any methylating agent, such as, but not limited to, SAME, 5-MTHF, folate, betaine (dimethylglycine), and trimethylglycine, can be included in the compositions of the present invention. The preferred methylating agents in the compositions of the present invention are SAME, 5-MTHF and betaine. These preferred methylating agents may be included in the compositions of the present invention either individually or in mixtures with themselves or with other methylating agents.

The phospholipids are a class of lipid molecules of particular importance in the function of the mammalian cell. They make up 75% of cell membranes, and therefore play an essential role in interactions between cells, including the communications that pass between neurons in the brain. Phospholipids are responsible for maintaining cell membrane fluidity. In other words, phospholipids allow cell receptors to be mobile over the surface of the cell, thereby enhancing cell-to-cell communication. This is important in all tissues, but especially so in the CNS. Phospholipids increase the effectiveness of existing levels of neurotransmitters, by ensuring that a maximum number of neurotransmitter molecules are able to interface with a receptor molecule.

There are two general classes of phospholipids, namely, phosphoglycerides and sphingolipids. The two groups of phospholipids are interrelated in both structure and function. Both are amphipathic, that is, they have a hydrophilic head composed of a phosphate group and a long hydrophobic tail composed of one or more fatty acid chains.

Attached to the phosphate head are various moieties that characterize the different phospholipids. It is the amphipathic nature of phospholipids that enables them to function in the cell membrane. Examples of phosphoglycerides that are important to CNS structure and function include phosphatidylserine, phosphatidylcholine, 5 phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, and cardiolipin. Phosphatidylserine is the precursor of phosphatidylcholine (FIG. 6), which is the single most abundant phospholipid in mammalian cell membranes. Examples of sphingolipids that are essential to the structure and function of the CNS include sphingomyelin, ceramide, gangliosides, and cerebrosides. The preferred phospholipids in the 10 compositions of the present invention are phosphatidylserine, phosphatidylcholine, and sphingomyelin. These preferred phospholipids may be included in the compositions of the present invention either individually or in mixtures with themselves or with other phospholipids.

Long-chain fatty acids serve as precursors of phospholipids in the body, and may 15 have independent neurochemical effects as well. Exogenously administered fatty acids are combined within the cell with phosphate moieties donated by ATP molecules to form phospholipids. The most important fatty acids in this regard are those over seventeen carbons in length, such as linoleic acid, linolenic acid, oleic acid, stearic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, lignoceric acid and nervonic acid.

20 The preferred fatty acids to be included in the compositions of the present invention are arachidonic acid, docosahexaenoic acid, and nervonic acid. These preferred fatty acids may be included in the compositions of the present invention either individually or in mixtures with themselves or with other fatty acids.

St. John's Wort (*Hypericum perforatum*) ("SJW") is an herbaceous plant native to Europe and North America. The plant contains several pharmacologically active compounds including hypericin. The exact mechanism of action of SJW is not clear, but infusions of the herb have been documented to inhibit catechol-o-methyl-transferase ("COMT"), and monoamine oxidase ("MAO") types A and B. These enzymes normally catabolize the catecholamines, including dopamine, serotonin, epinephrine, and norepinephrine. Blocking COMT and MAO A and B results in increased levels of serotonin and other catecholamines. St. John's Wort and hypericin fraction extracts of this herb inhibit MAO and COMT, therefore slowing the rate of breakdown of serotonin, the "feel good" neurotransmitter. This action is advantageous in almost all neurologic conditions because elevation of mood and reduction of perceived stress have beneficial effects on all body systems. In particular, St. John's Wort is indicated in affective disorders, such as depressive states. Its mechanism is similar to that of commonly prescribed MAO-inhibiting pharmaceuticals. Additionally, SJW may block the re-uptake of serotonin in the synaptic cleft, thus prolonging its effect. In this effect, SJW appears to duplicate the effects of SSRIs. Additionally, SJW may also affect the metabolism of other neurotransmitters such as dopamine, GABAA and GABAB. Numerous studies have documented the positive effect of SJW extracts on CNS function. Wincor, M. and Gutierrez, M., *St. John's Wort and the Treatment of Depressions*, Pharmacist, August, 1997, p. 88; Cicero, L., et al., *Can Depression Patients Be Treated with Worts?*, Drug Topics, September, 1997, p. 24; Tyler, V., *The Honest Herbal*, Haworth Press, Inc., New York, 1993, p. 275; Raffa, R., *Screen of Receptor and Uptake-Site Activity of Hypericin Component of St. John's Wort Reveals Sigma Receptor Binding*, Life Sci. 62(16), 1998, pp. PL265-70; Cott, J., *In Vitro Receptor Binding and Enzyme Inhibition by Hypericum*

Perforatum Extract, Pharmacopsychiatry, 30(2), 1997: pp. 108-12; Duke, J., et al.,
Western Herbal Medicine: Traditional Materia Medica, Complementary and Alternative
Veterinary Medicine, Schoen, A., Wynn, S., eds., Mosby, St. Louis, Mo. 1998, pp. 329,
357.

5 Tyrosine, the various phospholipids, S-AdoMet and 5-MTHF are available in pure
and stabilized forms for oral dosing. The active compounds in St. John's Wort are not
completely characterized but research has centered on hypericin, xanthones, and
flavonoids present in the plant leaves and flowers. A standardized extract of the herb
containing 0.3% hypericin is available. The dose of this extract for an adult human is
10 typically 300 mg per day. Although hypericin is not the only active compound in the
plant, it apparently is a marker for the fraction of the extract that does contain many if not
all of the active phytochemicals. Methods of analysis, both in vivo and in vitro, exist for
tyrosine, phospholipids, S-AdoMet, 5-MTHF, and hypericin.

Examples of the combinations of the present invention include:

- 15 1. Tyrosine and S-adenosylmethionine
2. Tyrosine and 5-methyltetrahydrofolate
3. Tyrosine, phosphatidylserine, and S-adenosylmethionine
4. St. John's Wort and 5-methyltetrahydrofolate
5. S-adenosylmethionine and St. John's Wort
20 6. Tyrosine and St. John's Wort
7. Tyrosine, S-adenosylmethionine, and St. John's Wort
8. St. John's Wort and phosphatidylserine
9. Phosphatidylcholine, phosphatidylinositol and sphingomyelin
10. Arachidonic acid, S-AdoMet and tyrosine
25 11. 5-MTHF and docosahexanoic acid

These compounds have different mechanisms of action, but all are crucial parts of biochemical reactions that result in a net increase in the levels of the important neurotransmitters dopamine and serotonin, and in improving the overall structure and function of the central nervous system.

5 It is expected that elements of the combinations of the present invention will work synergistically together because they have different, but complementary, mechanisms of action. For example, tyrosine will function to increase dopamine levels. The beneficial effects of such an increase would be multiplied if membrane fluidity were also increased, thereby facilitating interactions between the neurotransmitter and the receptor neuron.

10 Administration of a methylating agent, such as SAME, will increase membrane fluidity. Therefore, a composition combining tyrosine and SAME can be expected to function synergistically to increase dopamine levels and simultaneously enhance the effect of the dopamine on the target receptor neuron. Similarly, an increase in dopamine levels would be of limited value if the dopamine were quickly broken down by MAO and COMT. St.

15 John's Wort functions to increase net dopamine levels by increasing the half-life of this neurotransmitter. While tyrosine, SAME or St. John's Wort administration separately theoretically might each be expected to increase neuron function by 5-10%, a combination of two of these compounds theoretically might be expected to increase neuron function by 30-40%. As these examples show, the effects of combinations would

20 be expected to be more than merely additive.

Such synergy also enables the reduction of dosage levels for each compound. For example, the amount of SAME required to achieve a given improvement in neural function would be lower if the SAME were administered in combination with tyrosine or St. John's Wort than if it were given in isolation. This reduction in dose correspondingly

would reduce the potential for side effects. The compounds included in the composition of the present invention have wide margins of safety and low incidences of side effects in any case. Large doses of tyrosine can be associated with headaches, and overdoses of St. John's Wort have caused cases of photosensitization in humans and animals. At therapeutic levels, however, the incidence of side effects associated with these compounds is very low and certainly less than that of the prior art pharmaceuticals discussed above, such as the SSRIs. By combining compounds and therefore lowering necessary doses, the risk of side effects is even further reduced.

In many incidences of CNS dysfunction, moreover, the exact etiology can only be surmised. The compositions of the present invention are thus also superior to prior art treatments in that they can target numerous elements of CNS function, including cell membrane function (phospholipids, SAME), vascular function (5-MTHF), neurotransmitter production (tyrosine, SAME) and prevention of neurotransmitter degradation (St. John's Wort).

The compositions of the present invention can be administered by a variety of routes including, but not limited to: orally, transdermally, sublingually, intravenously, intramuscularly, rectally, and subcutaneously. Preferred daily doses for each of the compounds are as follows:

SAME (or many other methylating agents)

Total dose range: 15 mg to 5000 mg

Preferred small animal dose range: 15 mg to 600 mg

Preferred human dose range: 25 mg to 1000 mg

Preferred large animal dose range: 500 mg to 5000 mg

Tyrosine

Total dose range: 50 mg to 5000 mg

Preferred small animal dose range: 50 mg to 2500 mg

Preferred human dose range: 100 mg to 2500 mg

5 Preferred large animal dose range: 500 mg to 5000 mg

St. John's Wort

Total dose range: 50 mg to 5000 mg

Preferred small animal dose range: 50 mg to 500 mg

10 Preferred human dose range: 100 mg to 600 mg

Preferred large animal dose range: 500 mg to 5000 mg

Standardized St. John's Wort fraction containing hypericin

Total dose range: 0.25 mg to 500 mg

15 Preferred small animal dose range: 0.25 mg to 25 mg

Preferred human dose range: 2 mg to 25 mg

Preferred large animal dose range: 25 mg to 500 mg

5-methyltetrahydrofolate

20 Total dose range: 10 micrograms to 500 mg

Preferred small animal dose range: 10 micrograms to 200 mg

Preferred human dose range: 20 micrograms to 250 mg

Preferred large animal dose range: 30 micrograms to 500 mg

25 **Phospholipids** (example: phosphatidylserine or mixtures of phospholipids)

Total dose range: 5 mg to 5000 mg

Preferred small animal dose range: 5 mg to 500 mg

Preferred human dose range: 10 mg to 3000 mg

Preferred large animal dose range: 500 mg to 5000 mg

30

Fatty acids (example: arachidonic acid)

Total dose range: 2.5 mg to 2500 mg

Preferred small animal dose range: 2.5 mg to 250 mg

Preferred human dose range: 5 mg to 1500 mg

5 Preferred large animal dose range: 250 mg to 2500 mg

Having discussed the composition of the present invention, it will be more clearly perceived and better understood from the following specific examples which are intended to provide examples of the preferred embodiments and do not limit the present invention. Moreover, as stated above, the preferred components described in these examples may be replaced by or supplemented with the any of the components of the compositions of the invention described above.

15 EXAMPLE 1

A 72 year old woman has Parkinson's disease. This neurological dysfunction is associated with degeneration of the dopaminergic neurons of the substantia nigra and locus ceruleus of the brain. The symptoms of the disease (tremor, slowness of voluntary movement, facial rigidity and mental confusion) are a result of the decrease in dopamine in the substantia nigra. The patient is given a composition comprising 500 mg per day of tyrosine, 200 mg per day of SAME and 300 mg per day of phosphatidylcholine. The tyrosine functions as a precursor of dopamine, and its administration results in increased dopamine levels. The SAME and phosphatidylcholine result in enhanced neuronal cell membrane fluidity, thereby allowing the dopamine to be more effectively used. Phosphatidylcholine and SAME also enhance neuronal health and therefore support the remaining dopaminergic neurons and help maintain their secretion of dopamine.

This treatment for Parkinson's disease is an improvement over prior art therapies.

The current treatment of choice, which is the simultaneous administration of levadopa and carbidopa, provides a narrow therapeutic range (the effective dose is close to the dose at which adverse reactions such as dyskinesias, or involuntary movements, occur).

5 Levadopa and carbidopa are also contraindicated in persons with cardiovascular, renal or pulmonary disease, which are common in the elderly. The combination of tyrosine, SAME and phosphatidylcholine has a much wider therapeutic margin and no known contraindications.

EXAMPLE 2

10 A 9 year old neutered male cat has been "spraying" (urine marking) in his owner's house since the adoption of a second cat. The attending veterinarian diagnoses socially related inappropriate elimination, a condition caused by anxiety and mental conflict in the cat. Since this condition is the result of decreased serotonin levels, it can be treated by administering a combination of St. John's Wort and phospholipids. The
15 patient is given a composition comprising 100 mg per day of St. John's Wort containing 0.3% hypericin, and 100 mg per day of phosphatidylserine. The effect of the St. John's Wort is to increase the half-life of serotonin, thereby increasing its potential to affect a target neuron. The phosphatidylserine increases neuronal cell membrane fluidity and maximize the binding of serotonin to the post-synaptic receptors, further increasing this
20 desirable effect and allowing the dosage of St. John's Wort to be minimized.

This is an improvement over current therapy which consists of administering pharmaceuticals such as diazepam (a benzodiazapine), amitriptyline (a tricyclic antidepressant), megestrol acetate (a synthetic progesterone) or fluoxetine (a SSRI). These pharmaceuticals are associated with side effects and some are controlled

substances with abuse potential. Moreover, none is 100% effective, and there exists a need to develop additional alternatives to treat those animals that do not respond to these pharmaceuticals

EXAMPLE 3

5 A 65 year old man is recovering from an episode of cerebral hypoxia due to ischemia and infarction, commonly called a stroke. In this injury to the brain, an interruption in the supply of oxygen fatally injures brain cells (neurons). The resulting death of neurons causes deficits in neural function and leads to varying symptoms including paralysis, amnesia, and aphasia (loss of speech). Although the destroyed
10 neurons cannot be replaced, alternative pathways may develop that allow lost skills (walking, speech) to be relearned. Repairing the damaged CNS tissue and developing these alternative pathways requires the activity of non-neuronal cells in the CNS, which are collectively called glial cells. The administration of SAME and phospholipids would be very beneficial in the aftermath of cerebral injury. The patient is therefore given a
15 composition comprising 400 mg per day of SAME and 450 mg per day of mixed phospholipids (250 mg of phosphatidylcholine, 100 mg of phosphatidylserine and 100 mg of sphingomyelin). The phosphatidylserine is administered in this case because phospholipids make up 75% of the cell membrane and are therefore necessary for growth and function of glial cells, including astrocytes and microglial cells. SAME is an
20 essential participant in synthesis reactions in healing and growing CNS tissue. For example, it participates in the formation of phosphatidylcholine (the single most abundant phospholipid in cell membranes) from phosphatidylserine.

EXAMPLE 4

A 58 year old man has seasonal affective disorder, in which the decreasing hours of natural daylight in fall and winter months have a depressant effect on mood. This condition is associated with decreased amounts of serotonin. Current therapy for this condition includes the SSRI's, MAO inhibitors or administration of St. John's Wort alone. Because these approaches utilize the same mechanism of action, *i.e.*, they all slow the rate of serotonin degradation by blocking the action of COMT and/or MAO, they have additive effects in that they prolong the half life of serotonin. Therefore, using more than one of these compounds simultaneously can cause adverse effects by delaying the breakdown of serotonin too long, leading to nausea, vomiting, mental confusion and involuntary eye movements. Using MAO inhibitors and St. John's Wort together would not offer additional improvement in neural function, because the limiting factor of serotonin receptors on the post-synaptic cell is not addressed by either compound. By administering St. John's Wort in combination with phospholipids, however, serotonin levels can be elevated while receptor accessibility on the post-synaptic cell is also increased, thus insuring that almost every molecule of serotonin is used to good effect. The patient is therefore given a composition comprising 100 mg per day of St. John's Wort containing 0.3% hypericin and 150 mg per day of phosphatidylserine.

EXAMPLE 5

A 7 year old Standardbred gelding has developed signs of ataxia and muscle weakness due to infection with *Sarcocystis neurona*, or Equine Protozoal Myeloencephalitis. This disease is caused by aberrant parasite migration through the descending and ascending nerve pathways in the spinal cord and in the brain. Although the actual infection can apparently be terminated by long term administration of

antibiotics, the inventors are aware of no compound available for use in horses that will aid in healing the damage done by the parasitic migration. The disease leaves many horses with severe neurological deficits. The patient is given a composition comprising 800 mg per day of SAME and 1300 mg per day of neurohomologous phospholipids, including 900 mg per day of phosphatidylserine and 400 mg per day of sphingomyelin. As in Example 3, this composition would aid in the clearing away of damaged tissues and the growth and repair of glial cells that would facilitate the formation of alternative pathways, thereby enhancing recovery.

EXAMPLE 6

A 48 year old man is concerned because he has increased difficulty with cognitive function, specifically short-term memory and attention span. These symptoms are associated with several pathological changes in the CNS. One of these changes is the decreased neuronal mass that results as neurons succumb over time to toxins such as alcohol, hypoxia due to subclinical ischemia, and age-associated changes in cell membrane phospholipid content. Age associated cognitive dysfunction has also been linked to the brain's decreasing capacity to produce adequate amounts of neurotransmitters like dopamine and norepinephrine. Therefore, this patient is treated with a composition comprising 500 mg per day of tyrosine, 300 mg per day of phospholipids (200 mg per day of phosphatidylserine and 100 mg per day of phosphatidylcholine) and 200 mg per day of SAME. The tyrosine increases dopamine and norepinephrine levels in the brain. Simultaneously, the phospholipids and SAME enhance cell membrane function and facilitate neurotransmitter/receptor binding.

Many modifications may be made without departing from the basic spirit of the present invention. Accordingly, it will be appreciated by those skilled in the art that within the scope of the appended claims, the invention may be practiced other than has been specifically described herein. Hence, the attached claims are intended to cover the invention embodied in the claims and substantial equivalents thereto.

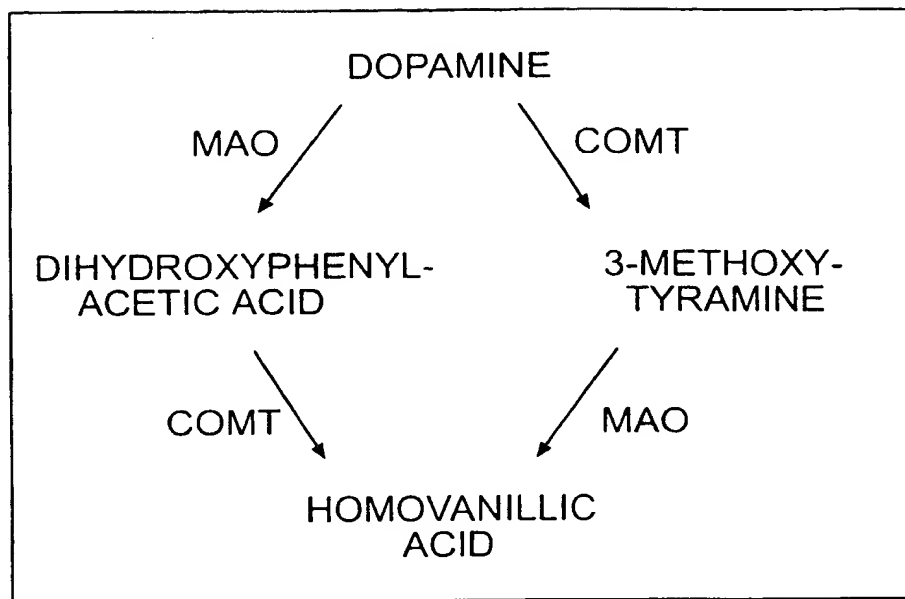
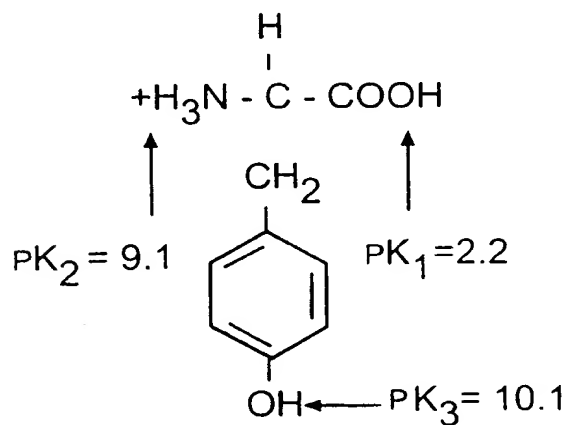
5

We claim:

1. A composition comprising any two or more of the following compounds:
tyrosine, one or more methylating agents, one or more phospholipids, one or more
5 fatty acids and St. John's Wort (*Hypericum perforatum*).
2. The composition of claim 1 in which the daily dose of tyrosine for humans or
animals ranges from 50 milligrams to 5000 milligrams.
3. The composition of claim 1 in which the methylating agent or agents is or are
selected from the group consisting of S-adenosylmethionine, 5-
10 methyltetrahydrofolate, folate, betaine (dimethylglycine), and trimethylglycine.
4. The composition of claim 3 in which one or more of the methylating agents is S-
adenosylmethionine and in which the daily dose for humans or animals ranges
from 15 milligrams to 5000 milligrams.
5. The composition of claim 3 in which one or more of the methylating agents is 5-
15 methyltetrahydrofolate and in which a daily dose for humans or animals ranges
from 10 micrograms to 500 milligrams.
6. The composition of claim 1 in which the phospholipid or phospholipids is or are
selected from the group consisting of phosphatidylserine, phosphatidylcholine,
phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol,
20 cardiolipin, sphingomyelin, ceramide, gangliosides, and cerebroside.
7. The composition of claim 6 in which the daily dose of the phospholipid or
phospholipids for humans or animals ranges from 5 milligrams to 5000
milligrams.
8. The composition of claim 1 in which the fatty acid or acids is or are selected from
25 the group consisting of all fatty acids over 17 carbons in length.

9. The composition of claim 8 in which the fatty acid or acids is or are selected from the group consisting of linoleic acid, linolenic acid, oleic acid, stearic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, lignoceric acid and nervonic acid.
- 5 10. The composition of claim 8 in which the daily dose of fatty acid or acids for humans or animals ranges from 2.5 milligrams to 2500 milligrams.
11. The composition of claim 1 in which the daily dose of St. John's Wort for humans or animals ranges from 50 milligrams to 5000 milligrams.
12. The composition of claim 1 in which the daily dose of the standardized extract of
10 St. John's Wort (hypericin fraction) for humans or animals ranges from 0.25 milligrams to 500 milligrams.
13. A method of administering the composition of the present invention to a human or other animal.
14. A method of regulating the neurotransmitters of a human or other animal by
15 administering therapeutically or prophylactically effective amounts of the compositions of the present invention.
15. A method of normalizing or improving the function of the central nervous system of a human or other animal by administering a therapeutically or prophylactically effective amount of the compositions of the present invention.

1/4

**FIG.1**

TYROSINE

FIG.2

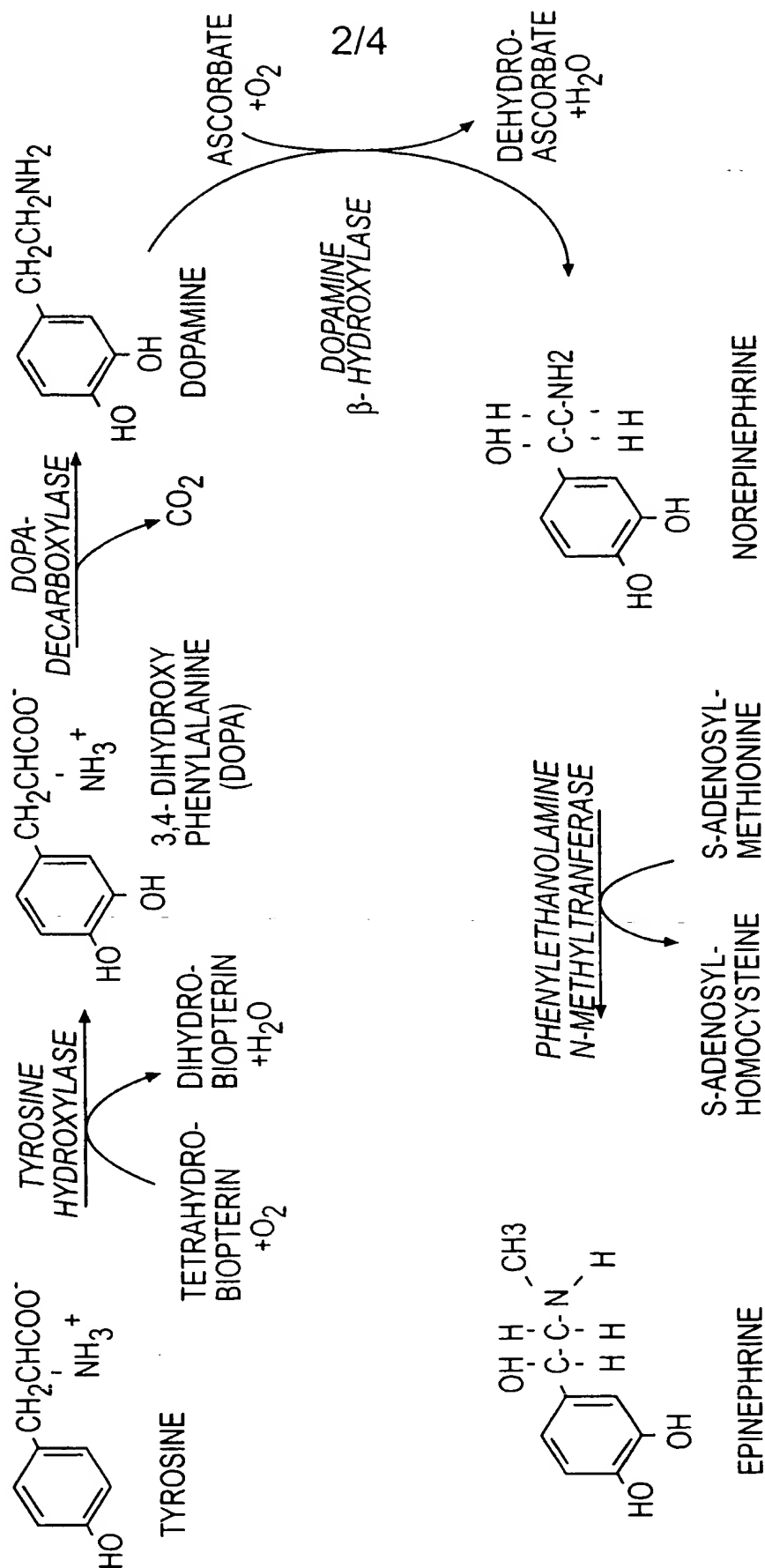
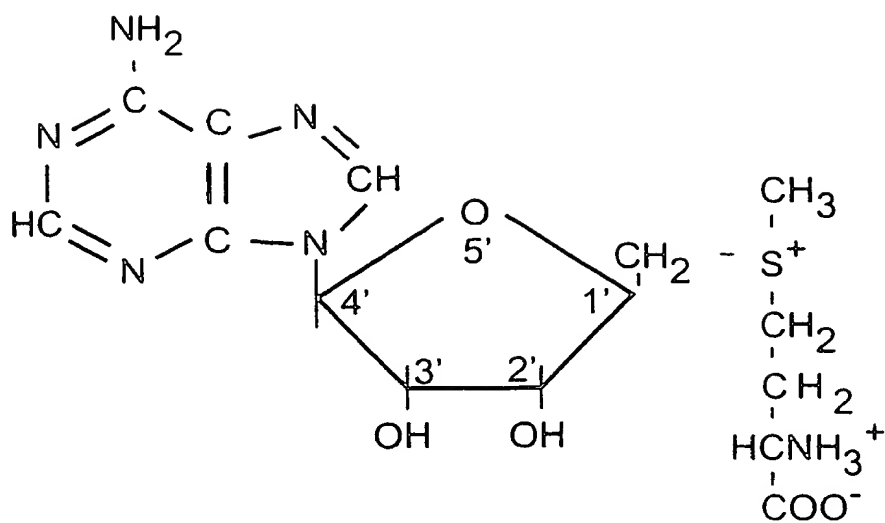


FIG.3

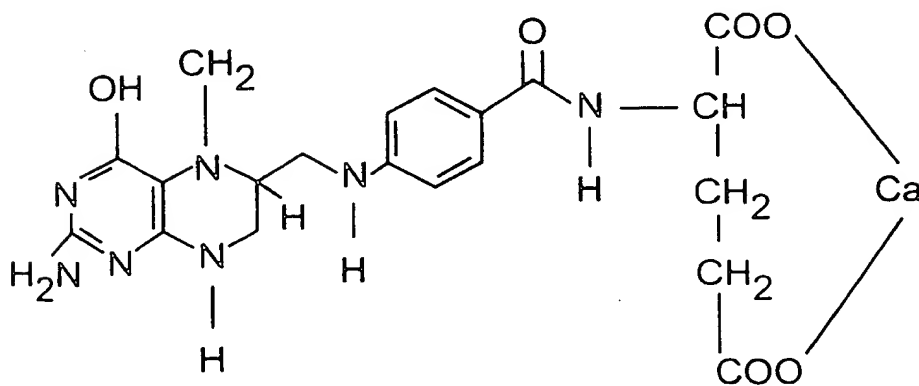
3/4



S-ADENOSYLMETHIONINE

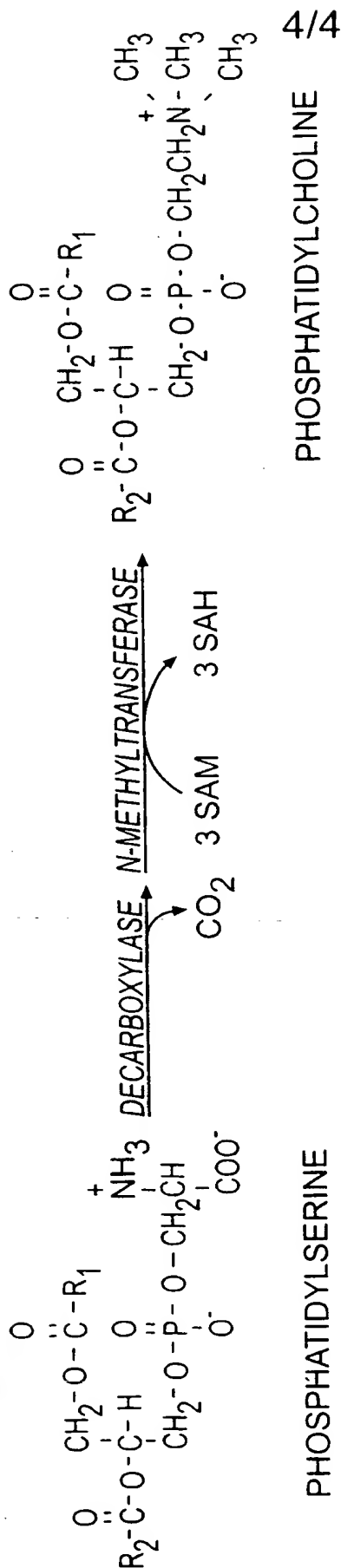
FIG. 4

5-METHYLTETRAHYDROFOLATE (5-MTHF)

*FIG. 5*

SUBSTITUTE SHEET (RULE 26)

SYNTHESIS OF PHOSPHOLIPIDIS



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DE NOVO SYNTHESIS OF PHOSPHATIDYLCHOLINE.
 (NOTE: SAM= S-ADENOSYLMETHIONINE; SAH= S-ADENOSYLHOMOCYSTEINE.)

FIG.6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/01581

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : 514/75, 78, 114, 249, 252, 266, 558, 567, 680

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/75, 78, 114, 249, 252, 266, 558, 567, 680

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NAPRALERT, HCAPLUS, REGISTRY, WPIDS, EMBASE.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database NAPRALERT on STN, (Columbus, OH, USA), SAN 1999:378, SCHMIDT, K. Antidepressant therapy with St. John's Wort. Therapiewoche. 1995, Vol. 2, pages 106-112, see entire document.	1, 11-13
X - A	Database HCAPLUS in STN, (Columbus, OH, USA), No. 127:252976, JP 09241131 A2 (NENDO KAGAKU KENKYSHO K.K.), abstract, 16 September 1997.	1-2, 14 --- 3-13, 15
X - A	Database WPIDS on STN, (Columbus, OH, USA), AN 96-114523, RU 2038073 C (ERMOLOVS, L. S.), abstract, 22 March 1996.	1, 8-9, 13 -- 2-7, 10-12, 14-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 MARCH 1999

Date of mailing of the international search report

22 APR 1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/01581

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A01N 57/00, 57/26, 43/58, 43/60, 43/90, 37/00, 37/12, 37/44, 35/00;

A61K 31/66, 31/685, 31/66, 31/495, 31/50, 31/52, 31/20, 31/195, 31/12

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